

# Dysplastic Nevus – Risk Factor or Disguise for Melanoma

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## ABSTRACT

*Dysplastic nevus is an acquired or hereditary nevus that clinically seems atypical and pathohistologically dysplastic. The term of dysplastic nevus has changed through history and even until now the dermatologists and pathologists have not found the same conclusion for name and definition of dysplastic nevus. Epidemiology of dysplastic nevus is different depending on geographic latitude, being three times higher in Australia than in Great Britain. Genetic factors play a role in etiology of dysplastic nevus but are still not well defined. UV radiation is indisputable main etiological factor in developing dysplastic nevus. Many studies confirm that children who have been using sun protection creams with SPF have less dysplastic nevi than those who did not. Nevus with geographic shape and muddy borders, dominantly macular, red to brown colored and has 5 mm or more in diameter is clinically dysplastic nevus. ABCDE rules count for dysplastic nevus as well as for melanoma but preferable diagnostic criteria for dysplastic nevus would be »ugly duckling sign«. Pathohistologic analysis is the key in confirming the diagnosis of dysplastic nevus. Great experience and knowledge in dermatopathology field is essential for pathologists to make a distinction between dysplastic nevus and melanoma in situ. Likewise great experience in dermatooncology field is essential in differentiating dysplastic nevus from other nevi. Surgical excision is the only therapy that should be done for dysplastic nevus. Regular follow up is highly recommended for patients with dysplastic nevus and syndrome naevi dysplastici. Education about sun protection measures and self-examination techniques is essential for all patients with dysplastic nevi and their family.*

**Key words:** dysplastic nevus, atypical nevus, dysplastic nevus syndrome, melanoma, dermatooncology

## Introduction

Dysplastic nevus is an acquired or hereditary nevus that clinically seems atypical and pathohistologically dysplastic. Many debates and controversies have been carried out until today about dysplastic nevus. Does it exist or not? Most melanoma occur »de novo« but 20–30% of melanoma arises from pigmented precursor, dysplastic nevus. Chen said that it is not important what one observes but what one believes<sup>1</sup>. There are two theories in which you can believe. Multistep tumorigenesis theory, which begins with normal melanocytes to hyperplasia to nevus then dysplastic nevus and finally melanoma. It is applicable for many carcinomas like colorectal carcinoma. Other theory describes dysplastic nevus as intermediate lesion that does not exist because neoplasms are alterations in DNA which are nonsequential and stochastic. Ackerman said: »In the realm of melanocytic neoplasms,

there are only four possible answers: nevus, melanoma, melanoma in association with a nevus, and I don't know«<sup>2</sup>.

## Nomenclature, epidemiology and etiology

The term of dysplastic nevus has changed through history and even until now the dermatologists and pathologists have not found the same conclusion for name and definition of dysplastic nevus. In 1800 Norris reported appearance of great number of nevi in members of two families in which two members died from melanoma. In 1974 Munro described clinical and microscopic features of atypical nevi in families with reported melanoma occurrence. The term B-K moles appears in 1978 when Clark recognized the first two families with atypical nevi whose surnames began with B and K<sup>3</sup>. The term familial

atypical multiple mole and melanoma syndrome was proposed by Fussaro in 1983. In 1985 Elder explained the theory of »nevus-melanoma« for sporadic dysplastic nevi as precursors of melanoma. Today most used nomenclature for dysplastic nevus is Clark's nevus, atypical mole and nevus with architectural disorder (with varying degrees of melanocytic atypia).

Atypical mole syndrome (AMS) had different criteria through history. Newton et al. made criteria in 1993. In 1990s Classical atypical mole syndrome included having more than 100 nevi, one nevus 8 mm in diameter or more and at least one lesion with atypical features. In 1992 National Institute of Health (NIH) brought Consensus of AMS with characteristics of occurrence of melanoma in one or more first or second degree relatives, having large number of melanocytic nevi, more than 50, some being atypical and variable in size and having melanocytic nevi that present certain histological features<sup>4</sup>.

Dysplastic nevus is relatively common in general population. Epidemiology of dysplastic nevus is different depending on geographic latitude, being 3 times higher in Australia than in Great Britain. Some authors reported prevalence ranging from 2–53% depending on the diagnostic criteria. The prevalence is much higher in patients with melanoma being 34–59%. Epidemiology of AMS depends on diagnostic criteria. NIH estimated that in 1985 about 32,000 individuals had AMS and familial melanoma in the United States of America and 3 million people had sporadic AMS<sup>4</sup>.

The etiology of dysplastic nevus is complex. It is interaction of multiple genes and environmental factors. Genetic factors are still not well defined. There are no certain genes or molecular mechanism which is key in development of dysplastic nevus. Loss of heterozygosity on chromosome 9p21 gene p16 has been detected in melanoma, dysplastic nevus and benign nevus<sup>5</sup>. Homozygotic deletion of p16 was found in melanoma and dysplastic nevus<sup>5</sup>. Mutation of genomic locus CKDN2A on chromosome 9p21 was found in melanoma but not in dysplastic nevus, so in families with mutation of CKDN2A nevus dysplasticus is independent risk factor for development of melanoma<sup>5</sup>. Other mutations of BRAF, PTEN, CDK4 genes were not found in dysplastic nevi but mutation of NRAS gene was confirmed in dysplastic nevus<sup>5</sup>. UV radiation is indisputable main etiological factor in developing dysplastic nevus. Intermittent sun exposure and sunburns in childhood are related with development of melanoma as well as dysplastic nevi. Many studies confirmed that children who have been using sun protection creams with Sun Protection Factor (SPF) have less dysplastic naevi than those who did not<sup>5</sup>. One study reported higher prevalence of dysplastic nevi in Australian than United Kingdom, but the incidence of dysplastic nevi on buttocks were the same<sup>5</sup>.

## Clinical Findings

Clinically a dysplastic nevus is most often nevus with geographic, polygonal or rhomboid shape and muddy borders, dominantly macular, red to brown colored and has

5 mm or more in diameter. »The fried egg« sign is described for dysplastic nevus with macular and central papular component. ABCDE rules count for dysplastic nevus as well as for melanoma being A-asymmetry, B-irregular borders, C-varied colour, D-diameter more than 6 mm, but preferable diagnostic criteria for dysplastic nevus would be »ugly duckling sign«. It is a nevus which »pops in« from other nevi on the patient's skin. Different clinical appearance of dysplastic nevi is possible in one patient and in one family. Patient usually during examination explains: »My father and grandfather are full of moles like me.« When asking about sun behavior patterns patient says: »I had many sunburns in childhood. Before nobody took care about sun protection behavior.« Other information like artificial sunbathing, time of day exposed to sun, outdoor hobbies and sun protective behavior can contribute in decision about excision and follow up of the patient. Topography of dysplastic nevi can be any. The most often localisation is trunk, especially the torso. It is important to search for dysplastic nevi on special sites like acral parts, scalp, foldings and buttocks. It is required to search for other solar damages on patient's skin like solar/senile lentiginos, precanceroses or skin cancer.

Dysplastic nevi are dynamic lesions, which mostly occur in puberty and may become more atypical in clinical appearance or can regress over time but majority of dysplastic nevi remain stable. Erythema in dysplastic nevus and regression of lesion are possible signs of development of melanoma.

## Pathohistological analysis and differential diagnosis

Pathohistological analysis is the key in confirming the diagnosis of dysplastic nevus. NIH and World Health Organisation made consensus on the major mandatory pathohistological criteria and minor criteria for the diagnosis of dysplastic nevus<sup>6</sup>. Major criteria include lentiginous or contiguous melanocytic hyperplasia and focal melanocytic atypia. For the diagnosis of dysplastic nevus there should be at least two minor criteria: »shoulder phenomenon«, fusion of epithelial cones, subepidermal concentric lamellar fibrosis and superficial perivascular lymphocytic inflammatory infiltrate. Great experience and knowledge in dermatopathology field is essential for pathologists to make a distinction between dysplastic nevus and melanoma in situ. Today melanoma is the most frequent cause of medicolegal lawsuit for pathologist<sup>7</sup>. Therefore overdiagnosing melanoma is more often than underestimation but has great consequences for the patients.

Differential diagnosis is wide ranging from seborrheic keratosis, dermatofibroma, traumatised mole, lentigo solaris, Meyerson nevus, nevus Spilus, blue nevus, pigmented actinic keratoses, basal cell carcinoma, squamous cell carcinoma and melanoma<sup>8</sup>. Likewise great experience in dermatooncology field is essential in differentiating dysplastic nevus from other nevi. Today non-invasive method dermatoscopy is very useful tool in every day dermatooncology practice. Kittler et al showed 49% improvement in diagnostic accuracy in meta-analysis of 27 studies<sup>9</sup>. It

is important to emphasise that great clinical experience is important in differentiating which lesions are »at the edge« of clinical diagnosis and where our eye is insufficient so dermatoscopy can be relevant.

## Conclusion

Surgical excision is the only therapy that should be done for dysplastic nevus. Prophylactic excisions of all clinically dysplastic nevi is not the solution. As it is known that 20–30% of all melanoma arise from nevus so prophylactic excisions would not prevent melanoma development. There are many patients who seek private physicians for multiple excisions of nevi which can give a patient a false sense of security. There is still increased risk for development of melanoma.

Regular follow up is highly recommended for patients with dysplastic nevus and AMS. It should be every 3–12

months depending on patient's risk to development of melanoma. Dermatoscopy increases the diagnostic accuracy and if possible it should be done on every patient's follow up. Education about sun protection measures and self-examination techniques is essential for all patients with dysplastic nevi and their family. Sun protection measures are not just using sun creams with SPF but also seeking shade, wearing protective clothes and sunglasses<sup>10–12</sup>. Use of sun creams with SPF reduces the incidence of precancerous and melanocytic nevi. Patients should not apply sun creams with SPF to prolong being on the sun. Usually patients are disappointed with not getting tanned but new life behavior and attitudes must be adopted. Giving patient few minutes more during examination and explaining him/her about UV light as »nevo-genic« factor and protection measures can contribute a lot to increase awareness and changes in sun behavior and attitudes.

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## DISPLASTIČNI NEVUS – RIZIČNI ČIMBENIK ILI MASKA MELANOMA

## SAŽETAK

Displastični nevus je stečeni ili hereditarni nevus koji je u kliničkoj slici atipičan te u patohistološkoj slici displastičan. Naziv displastičnog nevusa se mijenjao kroz povijest pa čak i do danas dermatolozi i patolozi nisu donijeli zajedničku odluku oko naziva i definicije displastičnog nevusa. Epidemiologija displastičnog nevusa ovisi o geografskoj širini te je tako displastični nevus 3 puta češći u stanovnika Australije nego Ujedinjenog Kraljevstva. U etiologiji displastičnog nevusa genima imaju ulogu no još nije razjašnjeno kakvu. Glavni vanjski etiološki čimbenik, koji dovodi do nastanka displastičnog nevusa, a je UV zračenje. Brojne studije su pokazale da djeca koja su u mladosti koristila kreme sa zaštitnim faktorom imaju manje displastičnih nevusa. Displastični nevus klinički ima geografski oblik s mutnim rubovima, dominantno makularna lezija, od crvene do smeđe boje i 5 mm ili veći u promjeru. ABCDE pravila su korisna u dijagnostici displastičnih nevusa iako se danas više koristi tzv »znak ružnog pačeta«. Dijagnoza se potvrđuje patohistološkom analizom. Potrebno je veliko iskustvo i znanje iz područja dermatopatologije kako bi se napravila granica između displastičnog nevusa i melanoma in situ. Jedini terapijski izbor je kirurška ekscizija suspektne displastičnog nevusa. Jako je bitno da bolesnici s displastičnim nevusima i sindromom displastičnih nevusa redovito dolaze na kontrolne preglede. Također je bitno bolesnicima pružiti edukaciju o mjerama zaštite na suncu i samopregledima kože.